

Synthesis of Crossed [2 + 2] Photocycloadducts: A Novel Approach to the Synthesis of Bridged Bicyclic Alkenes

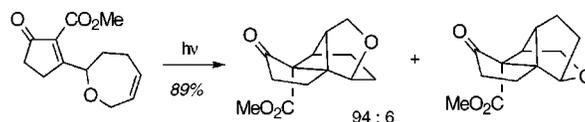
Michael T. Crimmins* and E. Bryan Hauser

Venable and Kenan Laboratories of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

crimmins@email.unc.edu

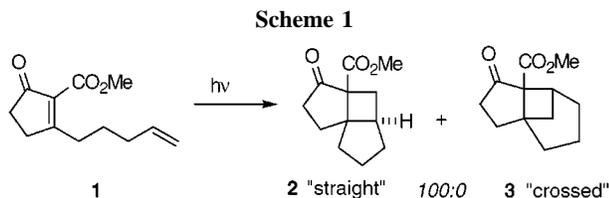
Received November 23, 1999

ABSTRACT



A solution to the synthesis of “crossed” intramolecular [2 + 2] photocycloadducts has been achieved. Through the use of a temporary heteroatom linker, the equivalent of a crossed photocycloadduct can be accessed at the expense of the normal “straight” adduct. Selectivity as high as 94:6 for the “crossed” adduct has been observed.

The intramolecular [2 + 2] photocycloaddition is a powerful reaction in the repertoire of the synthetic organic chemist,¹ particularly for the construction of quaternary carbon centers in sterically compressed environments. The recent applications of the intramolecular [2 + 2] photocycloaddition in such syntheses as ginkgolide B,² saudin,³ bilobalide,⁴ laurenene,⁵ and manzamine⁶ evidence its utility in the construction of sterically congested carbon frameworks. The normal mode of cycloaddition for enone **1** (Scheme 1) results in



high regioselectivity for the “straight” adduct **2**, with none of the “crossed” adduct **3** observed. Because of the high regioselectivity for the straight adduct, particularly when the enone is tethered to the olefin by three or four atoms, many examples of intramolecular photocycloadditions in the ap-

plication to the synthesis of spiro-fused and linearly-fused systems have been reported, including those noted above.

The excellent selectivity of intramolecular photocycloadditions is a result of geometric constraints and conformational bias imposed by substituents on the tether between the two π -bonds involved in the cycloaddition.⁷ The straight adduct is produced as a result of the preference for the initial formation of a five-membered ring in the cyclization of the

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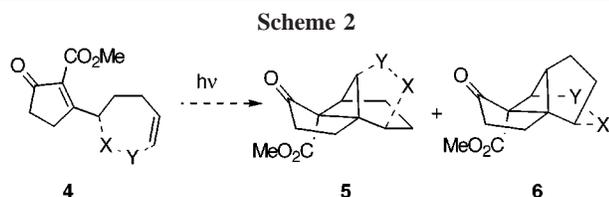
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triplet excited state to form the intermediate triplet biradical. Formation of the crossed adduct is disfavored since it would require initial cyclization to form either a six- or seven-membered ring.

If a method could be developed to allow selective access to the “crossed” photocycloadduct, a fundamentally unique approach to the synthesis of bridged bicyclic systems would be possible. We reasoned that if a temporary tether were incorporated into the photosubstrate as in enone **4**, the initial cyclization could proceed through the formation of a five-membered ring in the production of either the straight adduct **6** or the crossed adduct **5** (Scheme 2). Since either adduct



could be accessed through an initial five-membered ring formation, it might be possible to fine tune the tether to favor the crossed adduct by manipulating various structural features such as steric interactions, bond lengths, and bond angles. Subsequent cleavage of the temporary tether would result in the equivalent of a crossed adduct from a simple enone–alkene photocycloaddition.

Molecular mechanics calculations of a variety of possible substrates indicated that the cyclic ether **7** or the cyclic acetal **8** would possibly favor the crossed adduct (Figure 1). MM2

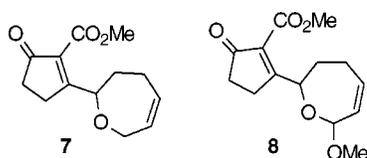


Figure 1. Substrates for crossed-selective photoadditions.

approximations indicated a difference of approximately 1.7–1.9 kcal per mol in favor of the transition state **9** leading to the crossed adduct in preference to transition state **10** to produce the straight adduct for enone **7** (Figure 2).⁸

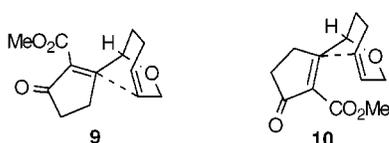
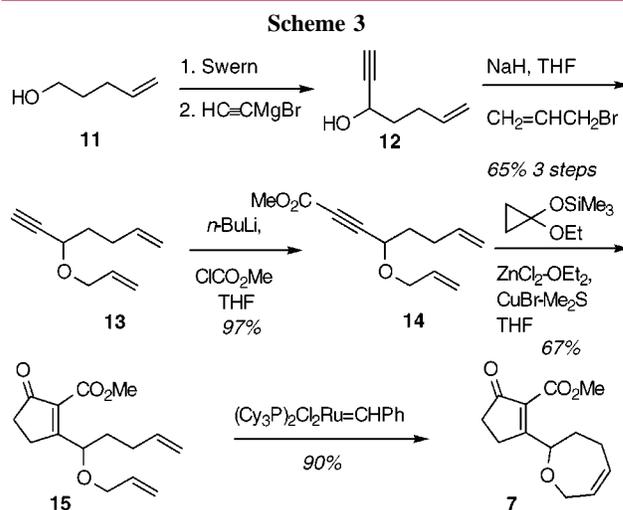
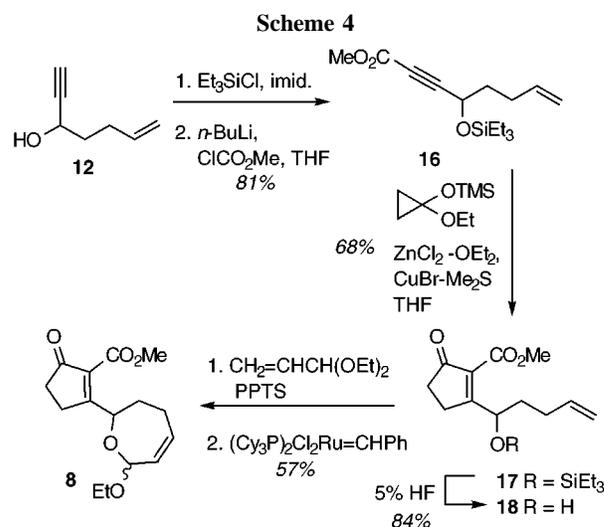


Figure 2. Transition states for photocycloaddition of **7**.



The synthesis of enone **7** is illustrated in Scheme 3. Oxidation of 4-penten-1-ol under Swern⁹ conditions was followed by addition of ethynylmagnesium bromide to produce acetylenic alcohol **12**. The alcohol was readily converted to allyl ether **13** by alkylation of the sodium alkoxide with allyl bromide.¹⁰ Carboxylation of the acetylene provided 97% of acetylenic ester **14** which was subsequently treated under our standard conjugate addition–cyclization conditions¹¹ to produce 2-carbalkoxycyclopentenone **15** in 67% yield. Finally, exposure of the diene **15** to 5 mol % of $(\text{Cy}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh}$ [40 °C, CH_2Cl_2] produced the desired photosubstrate **7** in 90% yield.¹²

Cyclic acetal **8** was prepared in a similar manner as shown in Scheme 4. Acetylenic alcohol **12** was protected as

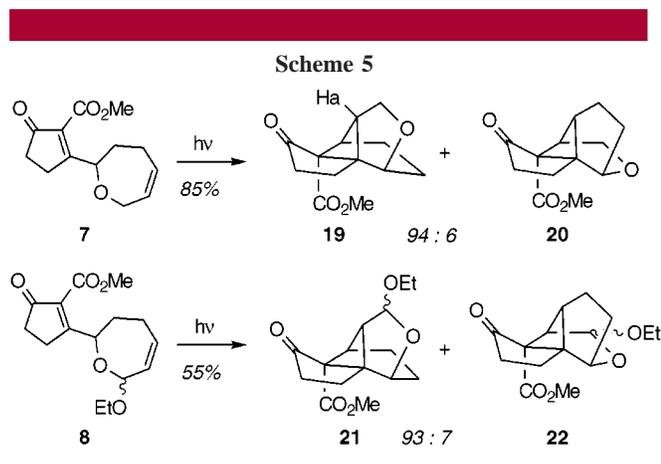


triethylsilyl ether **16**, and the acetylene was converted to acetylenic ester **16** in 81% overall yield. The acetylenic ester

(8) Energy minimizations were performed by restricting the distance between the enone carbon and the alkene carbon to 2.5 Å.

was transformed to the cyclopentenone as described for **14**, and removal of the triethylsilyl ether provided alcohol **18**. Alcohol **18** was exposed to acrolein diethyl acetal in the presence of catalytic PPTS, and the resultant mixed acetal was treated with Grubbs catalyst [5 mol % of $(\text{Cy}_3\text{P})_2\text{Cl}_2\text{-Ru}=\text{CHPh}$, 40 °C, CH_2Cl_2] to afford the desired cyclic acetal **8** in good overall yield.¹³

Irradiation of a solution of cyclopentenone **7** in 1:4 dichloromethane:hexanes with a 450 W Hanovia lamp filtered with a uranium glass sleeve (>350 nm) resulted in the production of a 94:6 mixture of two diastereomeric photocycloadducts **19** and **20** in 85% yield (Scheme 5).



Similarly, acetal **8** produced a 93:7 mixture of two regioisomeric products each as a 1:1 mixture of acetal isomers **21**:**22**. Structural proof of the individual isomers was obtained by a combination of one- and two-dimensional NMR experiments. Most critically, coupling and NOE interaction of Ha in **19** with the adjacent methylene group of the ether linkage confirmed the regiochemistry of the photoaddition of **7**. Final confirmation was obtained by a single-crystal X-ray analysis of crossed photocycloadduct **21** as illustrated in Figure 3.

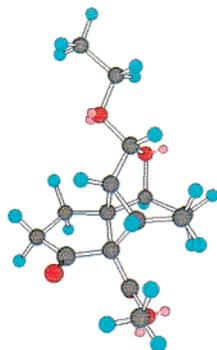
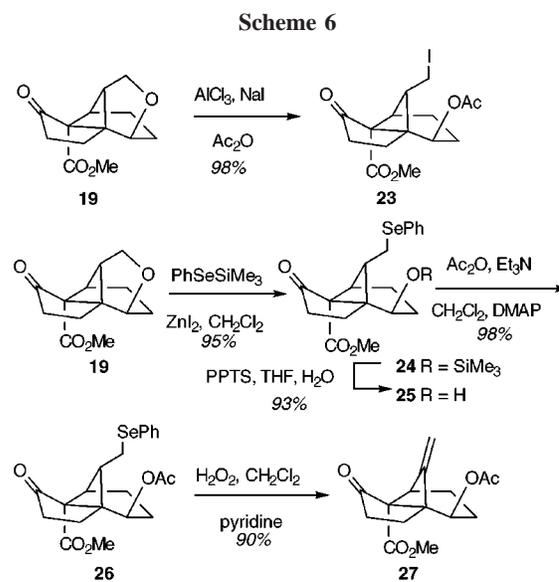


Figure 3.

With a viable approach to the preparation of crossed photoadducts available, it remained to establish a protocol

for the cleavage of the temporary linker. The ether linkage of photoadduct **19** was selectively cleaved to iodoacetate **23** in 98% yield by exposure of ether **19** to aluminum trichloride and sodium iodide¹⁴ followed by immediate trapping of the alcohol with acetic anhydride. The efficiency of this reaction prompted the investigation of similar ether fragmentations with other nucleophile–Lewis acid combinations. Exposure of ether **19** to phenyl trimethylsilylselenide and zinc iodide¹⁵ led to near quantitative conversion to selenide **24** which was readily hydrolyzed to alcohol **25** (Scheme 6). The alcohol



was protected as the acetate in 98% yield by treatment with acetic anhydride in the presence of Et_3N and DMAP. Subsequent exposure of selenide **26** to buffered hydrogen peroxide led to elimination of the selenoxide to give 90% of exocyclic olefin **27**. Alkene **27** is the equivalent of the hypothetical crossed photoadduct of allene **28** (Figure 4).

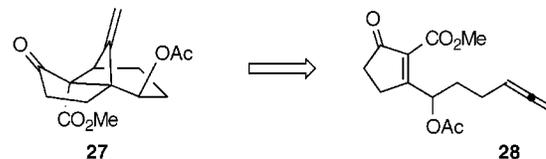


Figure 4. Hypothetical photoaddition of allene **28**.

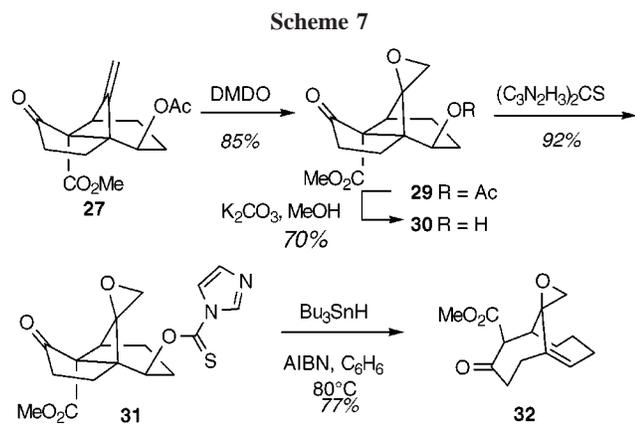
Thus, the approach described here provides efficient access to crossed photoadducts through an indirect strategy.

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Having developed a solution to the production of the crossed photocycloadduct, the selective cleavage of the cyclobutane was investigated. If the exocyclic olefin of cyclobutane **27** could be oxidized to a carbonyl, diol, or epoxide, and the acetoxy group converted to a radical precursor, cleavage of the cyclobutane to yield a bridgehead olefin might be possible. Molecular models indicate a nearly perfect antiperiplanar arrangement between the C–O bond of the acetate and the internal cyclobutane bond which would be cleaved. The added influence of the ester and ketone carbonyl groups could also help to weaken the cyclobutane bond and stabilize the developing radical center. Oxidation of the alkene proved difficult under standard conditions such as ozonolysis and osmium tetroxide dihydroxylation, but epoxidation could be effected with dimethyldioxirane¹⁶ to produce epoxide **29**. The acetate was removed with potassium carbonate in methanol to give the corresponding alcohol **30** that was readily converted to thiocarbamate **31** in 92% yield in the presence of thiocarbonyl diimidazole (Scheme 7). Exposure of thiocarbamate **31** to tributylstannane in



benzene resulted in selective cleavage of the more substituted cyclobutane bond, generating bicyclic alkene **32** in good yield.¹⁷ Alkene **32** contains much of the required functionality and all the carbon framework of the core of the novel natural product CP263,114 (Figure 5).¹⁸

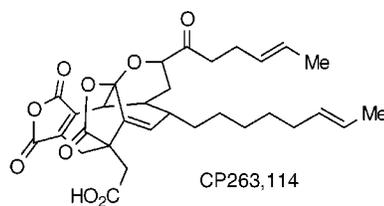


Figure 5. Structure of CP263,114.

An indirect solution to the preparation of the previously elusive crossed adducts of intramolecular photocycloadditions has been developed. The incorporation of a temporary tether allows the reversal of regioselectivity in the photoaddition and subsequent removal of the temporary linker gives the desired crossed photoadduct. The crossed cyclobutane adduct has also been further elaborated to a bridged bicyclic alkene through the use of a selective cyclobutylcarbinyl radical fragmentation. Application of this strategy to more highly substituted substrates for the synthesis of CP263,114 and other novel bicyclic compounds is in progress.

Acknowledgment. This work was supported by a research grant from the National Institutes of Health (GM38904).

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